



Clinical trial results:

A multicenter study to evaluate long-term safety and tolerability of open label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2018-004154-25 |
| Trial protocol | PL FR BG PT CZ ES HU HR DE AT IT FI |
| Global end of trial date | 29 December 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2024 |
| First version publication date | 06 July 2024 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CLCZ696B2319E1 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03785405 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG , 42 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG , 42 613241111, Novartis.email@Novartis.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 29 December 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 December 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To further evaluate long-term safety and tolerability of sacubitril/valsartan in eligible PANORAMA-HF participants receiving open-label sacubitril/valsartan

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment | 02 May 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Bulgaria: 2 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | Croatia: 4 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | Finland: 2 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | India: 10 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | Japan: 10 |
| Country: Number of subjects enrolled | Korea, Republic of: 13 |
| Country: Number of subjects enrolled | Lebanon: 9 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Portugal: 9 |
| Country: Number of subjects enrolled | Russian Federation: 3 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Singapore: 7 |
| Country: Number of subjects enrolled | South Africa: 8 |
| Country: Number of subjects enrolled | Spain: 11 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Taiwan: 6 |
| Country: Number of subjects enrolled | Thailand: 7 |
| Country: Number of subjects enrolled | Türkiye: 11 |
| Country: Number of subjects enrolled | United States: 51 |
| Worldwide total number of subjects | 215 |
| EEA total number of subjects | 72 |

Notes:

Subjects enrolled per age group

| | |
|-------------------------------------------|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 6 |
| Children (2-11 years) | 127 |
| Adolescents (12-17 years) | 66 |
| Adults (18-64 years) | 16 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

79 centers in 27 countries: Korea, Republic of, United States, Bulgaria, Italy, Thailand, Poland, Japan, Singapore, Israel, Turkey, Taiwan, South Africa, Portugal, Lebanon, Canada(2), Switzerland, Czech Republic, Croatia, Argentina, Hungary, India, Germany, France, Austria, Spain, Russia, Finland

Pre-assignment

Screening details:

A 36-hour washout after the last dose of study medication taken in the PANORAMA-HF core study (Visit 416) was required for all participants before starting Open Label Extension study medication.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Age Group 1 |

Arm description:

Patients 6 years and older receiving open label sacubitril/valsartan 3.1 mg/kg bid

| | |
|----------------------------------------|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | sacubitril/valsartan |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

sacubitril/valsartan 200mg bid

| | |
|----------------------------------------|----------------------|
| Investigational medicinal product name | sacubitril/valsartan |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Oral liquid |
| Routes of administration | Oral use |

Dosage and administration details:

sacubitril/valsartan 200mg bid

| | |
|----------------------------------------|----------------------|
| Investigational medicinal product name | sacubitril/valsartan |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

sacubitril/valsartan 200mg bid

| | |
|------------------|-------------|
| Arm title | Age Group 2 |
|------------------|-------------|

Arm description:

Patients 1 year to < 6 years receiving open label sacubitril/valsartan 3.1 mg/kg bid

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------------------------------------|----------------------|
| Investigational medicinal product name | sacubitril/valsartan |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: sacubitril/valsartan 200mg bid | |
| Investigational medicinal product name | sacubitril/valsartan |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Oral liquid |
| Routes of administration | Oral use |
| Dosage and administration details: sacubitril/valsartan 200mg bid | |
| Investigational medicinal product name | sacubitril/valsartan |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: sacubitril/valsartan 200mg bid | |

| Number of subjects in period 1 | Age Group 1 | Age Group 2 |
|---------------------------------------|-------------|-------------|
| Started | 130 | 85 |
| Completed | 92 | 74 |
| Not completed | 38 | 11 |
| Adverse event, serious fatal | 6 | 4 |
| Physician decision | 8 | 5 |
| Participant decision | 2 | - |
| Not available | 1 | - |
| Adverse event, non-fatal | 16 | 1 |
| Lost to follow-up | 1 | - |
| Guardian decision | 4 | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------------------------------------------------------------|-------------|
| Reporting group title | Age Group 1 |
| Reporting group description: | |
| Patients 6 years and older receiving open label sacubitril/valsartan 3.1 mg/kg bid | |
| Reporting group title | Age Group 2 |
| Reporting group description: | |
| Patients 1 year to < 6 years receiving open label sacubitril/valsartan 3.1 mg/kg bid | |

| Reporting group values | Age Group 1 | Age Group 2 | Total |
|----------------------------------------------------|-------------|-------------|-------|
| Number of subjects | 130 | 85 | 215 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 6 | 6 |
| Children (2-11 years) | 48 | 79 | 127 |
| Adolescents (12-17 years) | 66 | 0 | 66 |
| Adults (18-64 years) | 16 | 0 | 16 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 12.83 | 2.94 | |
| standard deviation | ± 3.864 | ± 1.149 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 60 | 49 | 109 |
| Male | 70 | 36 | 106 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 0 | 2 |
| White | 78 | 41 | 119 |
| Asian | 24 | 23 | 47 |
| Black or African American | 19 | 10 | 29 |
| Multiple | 0 | 4 | 4 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Unknown | 7 | 6 | 13 |

End points

End points reporting groups

| | |
|--------------------------------------------------------------------------------------|-------------|
| Reporting group title | Age Group 1 |
| Reporting group description: | |
| Patients 6 years and older receiving open label sacubitril/valsartan 3.1 mg/kg bid | |
| Reporting group title | Age Group 2 |
| Reporting group description: | |
| Patients 1 year to < 6 years receiving open label sacubitril/valsartan 3.1 mg/kg bid | |

Primary: Duration of drug exposure

| | |
|-----------------------------------------------------------------------------------------|------------------------------------------|
| End point title | Duration of drug exposure ^[1] |
| End point description: | |
| Median duration of exposure to sacubitril/valsartan (including temporary interruptions) | |
| End point type | Primary |
| End point timeframe: | |
| Up to 4.5 years | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome.

| End point values | Age Group 1 | Age Group 2 | | |
|-------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 130 | 85 | | |
| Units: Days | | | | |
| median (full range (min-max)) | 894 (23 to 1612) | 951 (62 to 1570) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Serious Adverse Events

| | |
|------------------------------------------------------------------------|-------------------------------------------------------------------|
| End point title | Number of participants with Serious Adverse Events ^[2] |
| End point description: | |
| Number of participants with at least one Serious Adverse Events (SAEs) | |
| End point type | Primary |
| End point timeframe: | |
| to end of study, up to 4.5 years | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome.

| End point values | Age Group 1 | Age Group 2 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 130 | 85 | | |
| Units: Participants | 59 | 25 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Adverse Events

| | |
|-----------------|-----------------------------------------------------------|
| End point title | Number of participants with Adverse Events ^[3] |
|-----------------|-----------------------------------------------------------|

End point description:

Number of participants with at least one Adverse Events (AEs)

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

to end of study, up to 4,5 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome.

| End point values | Age Group 1 | Age Group 2 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 130 | 85 | | |
| Units: Participants | 111 | 78 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 4.5 years

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Age group 1 (6 Years or more) |
|-----------------------|-------------------------------|

Reporting group description:

Age group 1 (6 Years or more)

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Age group 2 (1 to less than 6 years) |
|-----------------------|--------------------------------------|

Reporting group description:

Age group 2 (1 to less than 6 years)

| Serious adverse events | Age group 1 (6 Years or more) | Total | Age group 2 (1 to less than 6 years) |
|------------------------------------------------------|-------------------------------|-------------------|--------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 59 / 130 (45.38%) | 84 / 215 (39.07%) | 25 / 85 (29.41%) |
| number of deaths (all causes) | 7 | 11 | 4 |
| number of deaths resulting from adverse events | 1 | 1 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 4 / 215 (1.86%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 6 / 215 (2.79%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device site pain | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device site extravasation | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 5 / 130 (3.85%) | 5 / 215 (2.33%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Heart transplant rejection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 3 / 215 (1.40%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Atelectasis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device power source issue | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcus test positive | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus test positive | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Seroma | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incorrect dose administered | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cryptorchism | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital epiblepharon | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-------------------|------------------|----------------|
| Cardiac failure | | | |
| subjects affected / exposed | 15 / 130 (11.54%) | 18 / 215 (8.37%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 1 / 24 | 2 / 30 | 1 / 6 |
| deaths causally related to treatment / all | 1 / 3 | 1 / 5 | 0 / 2 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 6 / 215 (2.79%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 4 / 215 (1.86%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dilated cardiomyopathy | | | |
| subjects affected / exposed | 5 / 130 (3.85%) | 5 / 215 (2.33%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary valve stenosis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia induced cardiomyopathy | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 3 / 215 (1.40%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile convulsion | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Splenic cyst | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall haemorrhage | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 130 (2.31%) | 5 / 215 (2.33%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 3 / 215 (1.40%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Renal impairment | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc space narrowing | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 2 / 215 (0.93%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Lower respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Influenza | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 6 / 215 (2.79%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 215 (0.93%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 8 / 215 (3.72%) | 4 / 85 (4.71%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 5 / 130 (3.85%) | 9 / 215 (4.19%) | 4 / 85 (4.71%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 12 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia mycoplasmal | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypernatraemia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 215 (0.93%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 215 (0.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 215 (0.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Age group 1 (6 Years or more) | Total | Age group 2 (1 to less than 6 years) |
|-------------------------------------------------------|-------------------------------|--------------------|--------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 90 / 130 (69.23%) | 150 / 215 (69.77%) | 60 / 85 (70.59%) |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 13 / 130 (10.00%) | 14 / 215 (6.51%) | 1 / 85 (1.18%) |
| occurrences (all) | 16 | 17 | 1 |
| Vascular disorders | | | |

| | | | |
|--------------------------------------------------------------------|-------------------------|-------------------------|------------------------|
| Hypotension subjects affected / exposed occurrences (all) | 18 / 130 (13.85%) 26 | 21 / 215 (9.77%) 29 | 3 / 85 (3.53%) 3 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 14 / 130 (10.77%) 23 | 14 / 215 (6.51%) 23 | 0 / 85 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 15 / 130 (11.54%) 21 | 18 / 215 (8.37%) 24 | 3 / 85 (3.53%) 3 |
| General disorders and administration site conditions | | | |
| Pyrexia subjects affected / exposed occurrences (all) | 15 / 130 (11.54%) 23 | 37 / 215 (17.21%) 56 | 22 / 85 (25.88%) 33 |
| Chest pain subjects affected / exposed occurrences (all) | 8 / 130 (6.15%) 11 | 10 / 215 (4.65%) 13 | 2 / 85 (2.35%) 2 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 9 / 130 (6.92%) 17 | 18 / 215 (8.37%) 28 | 9 / 85 (10.59%) 11 |
| Abdominal pain subjects affected / exposed occurrences (all) | 10 / 130 (7.69%) 12 | 13 / 215 (6.05%) 15 | 3 / 85 (3.53%) 3 |
| Vomiting subjects affected / exposed occurrences (all) | 15 / 130 (11.54%) 20 | 27 / 215 (12.56%) 44 | 12 / 85 (14.12%) 24 |
| Nausea subjects affected / exposed occurrences (all) | 9 / 130 (6.92%) 9 | 10 / 215 (4.65%) 10 | 1 / 85 (1.18%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 6 / 130 (4.62%) 8 | 12 / 215 (5.58%) 19 | 6 / 85 (7.06%) 11 |
| Oropharyngeal pain | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 7 / 130 (5.38%) 8 | 9 / 215 (4.19%) 15 | 2 / 85 (2.35%) 7 |
| Dyspnoea subjects affected / exposed occurrences (all) | 10 / 130 (7.69%) 12 | 10 / 215 (4.65%) 12 | 0 / 85 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 20 / 130 (15.38%) 27 | 39 / 215 (18.14%) 58 | 19 / 85 (22.35%) 31 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 8 / 130 (6.15%) 8 | 10 / 215 (4.65%) 10 | 2 / 85 (2.35%) 2 |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 7 / 130 (5.38%) 8 | 14 / 215 (6.51%) 20 | 7 / 85 (8.24%) 12 |
| Influenza subjects affected / exposed occurrences (all) | 6 / 130 (4.62%) 8 | 14 / 215 (6.51%) 20 | 8 / 85 (9.41%) 12 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 130 (2.31%) 4 | 8 / 215 (3.72%) 14 | 5 / 85 (5.88%) 10 |
| COVID-19 subjects affected / exposed occurrences (all) | 23 / 130 (17.69%) 25 | 47 / 215 (21.86%) 51 | 24 / 85 (28.24%) 26 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 12 / 130 (9.23%) 21 | 26 / 215 (12.09%) 78 | 14 / 85 (16.47%) 57 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 8 / 130 (6.15%) 15 | 30 / 215 (13.95%) 57 | 22 / 85 (25.88%) 42 |
| Pharyngitis subjects affected / exposed occurrences (all) | 6 / 130 (4.62%) 7 | 11 / 215 (5.12%) 14 | 5 / 85 (5.88%) 7 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 September 2021 | The primary purpose of this protocol amendment was to extend the duration of the study. The original protocol was expected to end as early as May-2022 and no later than Dec-2022. In this amendment, the duration of the study was extended to ensure that study participants continued to receive age-appropriate study drug treatment (especially those requiring the pediatric formulations not currently available outside investigational use) and safety follow-up until the expected time when pediatric use of sacubitril/valsartan received local marketing authorization and became commercially available to participants. |
| 30 November 2021 | <p>On 26-Oct-2021, an urgent safety measure (USM) was implemented by Novartis in the PANORAMA-HF core study due to a quality issue with enalapril, the active comparator.</p> <p>The USM included the following:</p> <ul style="list-style-type: none">• Investigational medicinal product (IMP) dispensation was blocked in the IRT system by Novartis• All participants who were receiving study medication at the time the USM was initiated, had to discontinue study treatment by 31-Oct-2021 and change to local standard of care, respecting any required washout periods. These participants were to attend an unscheduled visit at the site by 31-Oct-2021, or as soon as possible thereafter, for safety and efficacy assessments.• It was requested for all patients to return IMP in their possession by 31-Oct-2021.• All IMP is to be removed from the sites for destruction per local practices. <p>As a result, not all the participants were on study drug treatment at PANORAMAHF Part 2 EOS visit (Visit 416). The purpose of the second protocol amendment was to amend the inclusion and exclusion criteria to allow participants impacted by the USM to enroll into this OLE study.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported